MS02 Infection and Disease/hot structures

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Control of phosphodiesterase activity in RbdA, a regulator of biofilm dispersal

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Abstract

Bacteria can exist as a sessile biofilm or in the planktonic, free-swimming form, the switching is regulated by nucleotide messenger c-di-GMP. Phosphodiesterases are required for c-di-GMP breakdown, leading to dispersal. RbdA (regulator of biofilm dispersal) of the opportunistic human pathogen Pseudomonas aeruginosa has been highlighted to be involved in a cascade responsible for the dispersal of biofilms, in addition to its phosphodiesterase domain, it contains a sensory PAS domain which is of further interest. Furthermore, this cascade of dispersal is responsive to redox potential and nitric oxide (NO). The full mechanism and function of proteins of this cascade are currently poorly understood with the overall aim of discovering treatments for antimicrobial tolerant *Pseudomonas aeruginosa* biofilm infections. These infections are the leading cause of death among cystic fibrosis sufferers. Previous data on the multi-domain membrane protein RbdA have shown involvement in NO-induced biofilm dispersal and allosteric GTP regulation. Here, we show that the diguanylate cyclase domain N-terminal to the phosphodiesterase is an inverse regulator of c-di-GMP hydrolysis. The crystallographic structure of this active, substrate-free, dimeric phosphodiesterase allows insight into the structural mechanism controlling this inhibition. This will springboard further research to characterise these diguanylate cyclase-phosphodiesterase double domain proteins and more broadly the sensing mechanism of PAS domains, particularly in response to RedOx. This will enable us to better understand the pathway of dispersal of bacterial biofilms.

Determination of PDE activity of RbdA constructs